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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,314	07/25/2003	Elisabeth Henriette Burger	116.003	1901

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,314	BURGER, ELISABETH HENRIETTE	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the reply received on December 14, 2006.

Claims 1-18 and 21-23 are pending in the application.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Claims 1-18 and 21-23 are presented for examination on the merits as they read upon Applicant's elected species, i.e., a resorbable bone substitute for in vivo implantation, comprising bone cement material, an antimicrobial agent [LLLFLLKKRKKRKY (a.k.a. DHVAR-5)] and a bone growth factor (TGFß),wherein the microbial agent has a fast release profile and the bone growth factor has a slow release profile.

New Grounds of Objection

Claim Objections

Claims 14 and 15 are objected to because of the following informalities: Claims 14 and 15 are identical. Appropriate correction is required, e.g., canceling one of them.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the

conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily,chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to resorbable bone substitute for in vivo implantation, comprising bone cement material, an antimicrobial agent and a bone growth factor, wherein the microbial agent has a fast release profile and the bone growth has a slow release profile. In regards to the "antimicrobial agent" term, this is a very broad generic statement defined in the disclosure (page 2, lines 16-23) as "any compound or preparation having a MIC (Minimal Inhibitory Concentration) of less than 10 mu.M. Examples of such compounds are not limited to antibiotics, antimicrobial proteins, such as lactoferrin, antimicrobial peptides (AMPs) and cholates. Therefore, there exists a plethora of such compounds, with divergent chemical structures, which are not adequately described and/or represented in the examples. By the same token, the term "bone cement material" (e.g., disclosure, page 1, lines 17-22 and page 2, lines 1-15) comprises plastics, pastes, calcium phosphate, particles and beads of polymers such as polylactic acid or polyglycolic acid and any other suitable preformed bone substitute material, however, the example provided is drawn only to Biobon (calcium phosphate) cement powder. In addition, the term "bone growth factors" is drawn to any compound or preparation (with any chemical structure therein) capable of enhancing the activity of the enzyme alkaline phosphatase in pre-osteoblastic bone cells (e.g., disclosure, page 2, lines 24-25 and page 3, lines 1-7). A mere statement that such compounds would be desirable for resorbable bone compositions does not sufficiently provide ample written description pages describing the full breadth of the resorbable bone compositions comprising antimicrobial agents and bone growth factors with release profiles as instantly claimed. The specification does provide examples of what qualify as compounds of the claimed invention (see, e.g, disclosure, pages 17-20), however, these are limited to LLLFLLKKRKKRKY (a.k.a. DHVAR-5) with TGFß and do not encompass any other combinations of the broad claim comprising bone cement

material, an antimicrobial agent with fast release profile and a bone growth factor with slow release profile. As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 1 is a broad generic with respect all possible compounds encompassed by the claims. The possible structural variations are open to any kind of chemical compositions that have resorbable bone cement, antimicrobial and bone growth promoter activities. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of resorbable bone substitutes beside the one made of BiobonR cement powder, an antimicrobial agent of fast release profile LLLFLLKKRKKRKY (a.k.a. DHVAR-5) and the bone growth factor of slow release TGFß and does not encompass any other cement powders, antimicrobial agents and bone growth factors. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide

adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claims 1-8 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the invention. The claims are drawn to resorbable bone substitute for in vivo implantation, comprising bone cement material, an antimicrobial agent and a bone growth factor, wherein the microbial agent has a fast release profile and the bone growth has a slow release profile.

State of the prior art. At the time the invention was made, Burger et al. taught compositions comprising hydroxyapatite and LLLFLLKKRKKRKY which were of slow release (e.g., page 1, lines 1-5). This is reflected also by Applicant's statements in the reply of December 14, 2006, which also substantiate that Burger et al. describe a slow release antimicrobial peptide (e.g, page 7, lines 16-20 of Applicant's response) and Applicant's statements in the disclosure that Constatino et al. teach antibiotic agent and bone growth factor with a similar, relatively slow profile (e.g., disclosure, page 3, lines 8-24). Applicant also states that, as of 1996, there was prejudice against the use of antibiotics because of the risk of developing antibiotic resistant microorganisms at the

location of insertion of bone cement and secondary infection (Winiger et al. pages 2675 and 2678). However, the Burger et al. patent application, subsequently published, claims prevention and treatment of infection using antibiotic peptide LLLFLLKKRKKRKY (e.g., claims and abstract).

Breadth of the claims. The claims are extremely broad, encompassing resorbable bone substitute of any kind of biocompatible material for in vivo implantation, with any kind of antimicrobial agent (regardless of structure) having a fast release profile and any kind of bone growth factor (regardless of structure) having a slow release profile.

Working examples. The working example provided uses a resorbable bone substitute comprising BiobonR (cement powder), antimicrobial agent of fast release profile (LLLFLLKKRKKRKY) and bone growth factor (TGFß) of slow release profile.

Guidance in the specification. The specification provides little guidance regarding the making of the claimed compositions. The specification refers generally to resorbable bone substitutes with fast release profile of the antimicrobial agent, however, Burger et al.teach resorbable bone substitutes with the same constituents (e.g., hydroxyapatite and antimicrobial agent LLFLLKKRKKRKY (page 1, 1st paragraph and claims of Burger et al.) which are of slow release profile. Applicant's response of 12/14/06, page 7, lines 4-6 and 16-18) also highlights that Burger et al. is not prior art over the instant invention because the resulting compositions in Burger et al. are of slow release profile. Applicant's response of 12/14/06 also points out that Constantino describes slow release of antibiotics from bone cement and NOT fast release antibiotic

(Applicant's response of 12/14/06, page 7, lines 12-15). In addition, and more importantly, Applicant's own disclosure teaches that it has been found that antimicrobial peptides "show the required slow release profile" when incorporated in calcium phosphate-based curable bone cements (page 13, lines 11-18) and that the skilled person will know the proper ratios of the bone resorbable substitutes. Given the contradicting statements, including within the disclosure,regarding whether the antimicrobial peptides are of "slow" or "fast release profile", it is deemed that the specification does not provide sufficient guidance for one of ordinary skill in the art to arrive at such antimicrobial-containing "fast release profile" bone cements. There is no specific guidance regarding how to make the wide array of bone substitutes wherein such compositions have a fast release profile for the antibiotics/antimicrobials and a slow release profile for the bone growth factors.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). In the instant application, Applicant has not disclosed how the instant compositions made by mixing (e.g., claim 17) differ from the disclosed procedures of Constantino et al. (e.g., page 12, lines 4-17, claim 92) and Burger et al., (e.g., pages 7-9) and even from the 'slow release profile antimicrobials' taught within their own disclosure (e.g., page 13, lines 11-18) and how one skilled in the art would arrive at them.

Amount of experimentation necessary. Applicants have identified an interesting resorbable bone composition, however, given the divergent characterization of Applicant's own prior art, arguments with regards to the release profile for, e.g., a

hydroxyapatite composition comprising LLLFLLKKRKKRKY ("slow profile" in Burger et al. [and disclosure, page 13, lines 11-18]) vis-à-vis "fast profile" in the instant application, e.g., claim 1), essentially the work required to ultimately develop the instant compositions has been left for others.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to make the claimed compositions.

New Grounds of Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 and 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is rendered vague and indefinite because at lines 3-5, the limitation "wherein the microbial agent has a fast release profile, and the bone growth factor has a slow release profile" does not have well defined metes and bounds since 'fast' and 'slow' are relative terms and it is not clear how 'fast' or 'slow' the release profiles need to be in order to fulfill the instantly cited limitation. Please note that, in order to overcome this rejection, it is suggested to incorporate the disclosure definitions (page 5, lines 1-14) for these terms within the instant claim limitations.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13, 16-18 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Constantino et al. (WO 96/39202) [citation B in the IDS of 07/03] in view of Burger et al. (WO 00/01427) [citation D in the IDS of 07/03].

Constantino et al. teach a resorbable bone substitute for in vivo implantation, comprising bone cement material, an antimicrobial (antibiotic) agent, and bone growth factors such as TGFß and albumin (e.g., pages 17-18, page 31, last line, pages 32, page 33, lines 1-21), and forming a liquid phase with a protein carrier protein such as albumin and bone growth factors (see, e.g., page 32, lines 24-28, page 33, lines 1-28 and page 34, lines 1-4, page 35, lines 3-28, page 36, lines 1-12, page 37, lines 1-12). The bone growth factor may be from about 10-50 μg to about 100-500 μg for cm^3 of the formulation (e.g., page 35, lines 17-21, page 37, lines 8-12). Please note that TGFß necessarily reads upon having a slow release profile within the instantly claimed composition.

Constantino et al. do not teach a bone substitute wherein the antimicrobial agent is LLLFLLKKRKKRKY.

Burger et al. teach a resorbable bone substitute for in vivo implantation, comprising bone cement material, an antimicrobial agent (LLLFLLKKRKKRKY) (e.g., claim 23, page 1, lines 6-28; page 4, lines 19-21 and page 6, lines 6-25) and albumin as a protein carrier protein to hold the antimicrobial peptide(s) in solution (page 6, lines 26-32). Please note that the antimicrobial agent LLLFLLKKRKKRKY necessarily reads upon having a fast release profile.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Constantino et al. by using the antimicrobial peptide LLLFLLKKRKKRKY as taught by Burger et al. The skilled artisan would have been motivated to do so because Burger et al. teach that LLLFLLKKRKKRKY has low toxicity and a wide spectrum of antibacterial and antifungal activity, even against methycillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* (which is particularly dangerous in the case of osteomyelitis) and *amphotericin-B-resistant Candida Albicans* (see, e.g., page 1, lines 18-23; page 6, lines 10-15). There would have been a reasonable expectation of success, given that Constantino et al. teach a biocompatible hydroxyapatite as the bone cement with a growth factor and an antimicrobial (e.g., Constatino et al., page 13, lines 20-26; page 18, lines 10-21; page 43, lines 26-28 and page 44, lines 1-5) and given that bone growth factors such as TGFß were known to cause induction of new bone formation upon in vivo implantation as taught by Constantino et al. (e.g., page 35, lines 3-21) and because Burger et al. teach a biocompatible hydroxyapatite as the bone cement with an the antimicrobial LLLFLLKKRKKRKY, which is effective against infections which are

difficult to treat due to bacteria or fungi acquired-resistance. The adjustment of particular conventional working conditions [e.g., determining concentrations of the active ingredients, volume ratios of the mixing solutions, making kits thereof and/or making the composition by mixing the bone growth factor with albumin in a liquid medium and adding the antimicrobial peptide in a liquid medium as well (e.g., Constantino et al., page 35, lines 17-21, page 37, lines 8-12, claims 102, 115-118, 120-121 and Burger et al., e.g., page 7, lines 3-15).)] within such resorbable bone compositions, is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant argues that Constantino describes a slow release hydroxyapatite bone cement (for both antimicrobial and bone growth factor) and that Burger also describes a slow release antimicrobial peptide (See first paragraph, page 1). Applicant's arguments have been considered, yet not deemed persuasive because neither Constantino nor Burger provide a definition for such release profile. Additionally, the claimed compositions within both references appear to be structurally equivalent to those instantly claimed with regards to the antimicrobial agent or bone growth factor in addition with the bone cement and therefore would necessarily read upon a fast release profile and slow release profile respectively.

Applicant provides Exhibit 1, an article by Wininger et al. (Antimicrobial Agents and Chemotherapy, December 1996) in order to provide evidence that there was prejudice against the use of antibiotics because of the risk of developing antibiotic resistant microorganisms at the location of insertion of bone cement. Applicant's arguments and evidence have been considered by Examiner, however, the reference is not commensurate in scope with the claims and does not address the closest prior art (i.e., the resorbable bone cements of Constatino and Burger). In addition, e.g., Burger et al. ((WO 00/01427) teach prevention and treatment of osteomyelitis with resorbable bone cements comprising LLLFLLKKRKKRKY (e.g., abstract and page 1) and therefore evidence the effective use of antibiotics/antimicrobials within resorbable bone inserts.

Claims 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Constantino et al. (WO 96/39202) [citation B in the IDS of 07/03] in view of Burger et al. (WO 00/01427) [citation D in the IDS of 07/03] and in view of Van Niew Amerongen et al. (WO 01/56627).

Constantino et al. and Burger et al. are relied upon as above. Constantino et al. and Burger et al. do not teach coating solid bone cement particles of biocompatible resorbable material wherein the bone growth factor is incorporated in the particles and the coat comprises antimicrobial agent.

Van Nieuw Amerongen et al. (WO 01/56627) teach the antimicrobial agent LLLFLLKKRKKRKY (e.g., claim 5, Tables 1-2) for coating implants composed, e.g., of

apatites or cement in order to prevent/inhibit tissue loss and bone degradation around the implants (e.g., page 9-19).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition comprising resorbable bone and TGFß of Constantino et al. by using the antimicrobial LLLFLLKKRKKRKY and specifically by coating the antimicrobial as taught by Van Nieuw Amerongen et al. (WO 01/56627). The skilled artisan would have been motivated to do so because Van Niew Amerongen et al. teach coating implants made of apatites and cements (page 1, lines 5-20) with LLLFLLKKRKKRKY (e.g., page 9-10). There would have been a reasonable expectation of success, given that the antimicrobial activity of LLLFLLKKRKKRKY was maintained after coating as taught by Van Niew Amerongen et al. (e.g., page 9, lines 9-21; pages 10-11, claims 6-10). Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Rejection maintained

Claims 1-5, 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (US 6,485,751) in view of Van Nieuw Amerongen et al. (WO 01/56627).

Wang teaches a resorbable bone substitute for in vivo implantation, comprising bone cement material, an antimicrobial (antibiotic) agent and a bone growth factor such as TGFß (e.g., Fig. 1, column 1, lines 60-67, column 2, lines 5-37; column 4, lines 65-67 and column 5, lines 1-4). Please note that TGFß having a slow release profile necessarily reads upon the instantly claimed composition.

Wang does not teach the antimicrobial agent being LLLFLLKKRKKRKY (SEQ ID NO. 4) or an antimicrobial agent with fast release profile.

Van Nieuw Amerongen et al. (WO 01/56627) teach the antimicrobial agent LLLFLLKKRKKRKY (e.g., claim 5, Tables 1-2) for coating implants composed, e.g., of apatites or cement in order to prevent/inhibit tissue loss and bone degradation around the implants (e.g., page 9-19). Please note that having a fast release profile necessarily reads upon such antimicrobial agent composition.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the apatite cement composition of Wang by utilizing the antimicrobial agent LLLFLLKKRKKRKY as taught by Van Nieuw Amerongen et al. The skilled artisan would have been motivated to do so because Wang teaches bone cement materials with antibiotics for curing infection (column 4, lines 65-67, column 5, line 1), because LLLFLLKKRKKRKY was known to be used for infections resistant against most common antibiotics (e.g. page 1, lines 19-25, page 2, lines 8-38, claims 6-10) and because Van Nieuw Aromgen et al. teach that implants (including those made of cement and/or apatites, e.g., page 1, lines 18) may cause infections that are highly resistant against usual antimicrobial agents (page 2, lines 8-27). There would have been a reasonable expectation of success, given that LLLFLLKKRKKRKY was known to have a broad spectrum of action as taught by Van Nieuw Aromgen et al. (see Tables 1-2 for DHVAR-5). The adjustment of particular conventional working conditions [e.g., determining the amount of bone growth factor/antimicrobial peptide added within such bone substitute composition] is deemed merely a matter of judicious selection and

routine optimization that is well within the purview of the skilled artisan. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant argues that Wang does not teach a resorbable bone substitute having an antibiotic with fast release profile and a bone growth factor with a slow release profile and it is this unique combination that enables the implantation site to be cleaned of microorganisms and for creating conditions to regenerate bone material using a slow release growth factor.

Applicants arguments have been carefully considered by Examiner, but not deemed persuasive because neither Van Nieuw Amerongen nor Wang teach a specific desorption rate (i.e., release profile) and there is nothing of record to show that the prior art cited would have arrived to a structurally different invention from the instant invention, as claimed.

Conclusion

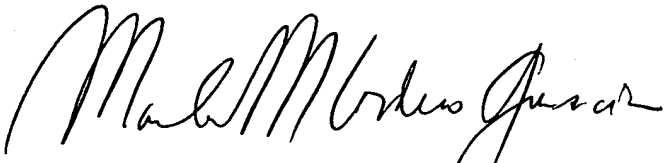
No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Marcela M Cordero Garcia, PhD
Patent Examiner
Art Unit 1654

MMCG 03/07